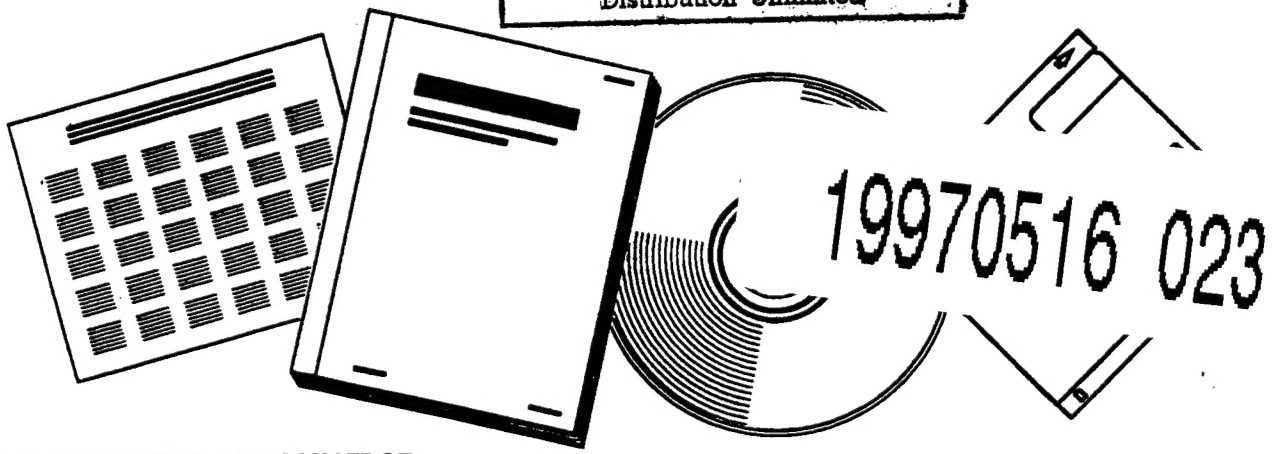
PB93-109957

PERMISSIBLE EXPOSURE LEVELS AND EMERGENCY EXPOSURE GUIDANCE LEVELS FOR SELECTED AIRBORNE CONTAMINANTS

NATIONAL RESEARCH COUNCIL
WASHINGTON, D.C.

1991



U.S. DEPARTMENT OF COMMERCE
National Technical Information Service

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

PB93-109957

2. REPORT DATE
1991

3. REPORT TYPE AND DATES COVERED
Final

4. TITLE AND SUBTITLE

Permissible Exposure Levels and Emergency Exposure Guidance Levels for Selected Airborne Contaminants

5. FUNDING NUMBERS

Contract No.
DAMD 17-89-C-9086

6. AUTHOR(S)

Subcommittee on Permissible Exposure Levels

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

National Research Council
2101 Constitution Ave., N.W.
Washington, DC 20418

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

Board on Environmental Studies & Toxicology

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

The U.S. Navy requested that the National Research Council's Committee on Toxicology recommend permissible exposure levels (PELs) for zinc dimethyldithiocarbamate (ziram) and ethylhexyl nitrate. No exposure levels for these compounds have been recommended either by the Occupational Safety and Health Administration or by the American Conference of Governmental Industrial Hygienists. The U.S. Army's Surgeon General's office also requested the 2-min emergency exposure guidance levels (EEGLs) for hydrogen chloride because of the Army's concern for the short-term high-level exposure of soldiers to hydrogen chloride vapors released during firing of various rocket motors and missiles. In response to these requests, the Committee on Toxicology set up the Subcommittee on Permissible Exposure Levels. The subcommittee, whose expertise is in toxicology, inhalation toxicology, genetics, biostatistics, medicine, and pathology, evaluated the toxicity data on ziram, ethylhexyl nitrate, and hydrogen chloride. In addition to the recommendations for PELs for ziram and ethylhexyl nitrate and EEGLs for hydrogen chloride, the subcommittee has identified deficiencies in the data and made recommendations for additional research. The subcommittee believes that the recommended exposure levels will provide adequate protection for workers and soldiers from these chemicals.

14. SUBJECT TERMS

permissible exposure levels (PELs), emergency exposure guidance levels (EEGLs), hydrogen chloride, zinc dimethyldithiocarbamate (ziram), ethylhexyl nitrate,

15. NUMBER OF PAGES
52

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	

Permissible Exposure Levels and Immediately Exposure Guidance Levels for Selected Airborne Contaminants

Permissible Exposure Levels and Emergency Exposure Guidance Levels for Selected Airborne Contaminants

Subcommittee on Permissible Exposure Levels
Committee on Toxicology

Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council

NATIONAL ACADEMY PRESS
Washington, D.C. 1991

NATIONAL ACADEMY PRESS 2101 Constitution Ave., N.W., Washington, D.C. 20418

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The project was supported by the U.S. Army under contract No. DAMD 17-89-C-9086.

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Printed in the United States of America

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Acknowledgments

The subcommittee is thankful to Bruce H. Kroening (Eastman Kodak Company) for his review and summaries of papers and assistance in preparing the analysis of hydrogen chloride; the subcommittee also thanks Ralph C. Reynolds, David P. Richardson, and Wayne M. Lednar (Eastman Kodak Company) for their review and comments on hydrogen chloride.

Preface

The U.S. Navy's Assistant Chief for Fleet Readiness and Support requested that the National Research Council's Committee on Toxicology recommend permissible exposure levels (PELs) for zinc dimethyldithiocarbamate (ziram) and ethylhexyl nitrate. Ziram is used by the Navy as a minor additive in antifouling coating systems, and ethylhexyl nitrate is used as a fuel additive. No exposure levels for these compounds have been recommended either by the Occupational Safety and Health Administration or by the American Conference of Governmental Industrial Hygienists. The U.S. Army's Surgeon General's office also requested the 2-min emergency exposure guidance levels (EEGLs) for hydrogen chloride because of the Army's concern for the short-term high-level exposure of soldiers to hydrogen chloride vapors released during firing of various rocket motors and missiles.

In response to these requests, the Committee on Toxicology set up the Subcommittee on Permissible Exposure Levels. The subcommittee, whose expertise is in toxicology, inhalation toxicology, genetics, biostatistics, medicine, and pathology, evaluated the toxicity data on ziram, ethylhexyl nitrate, and hydrogen chloride. In addition to the recommendations for PELs for ziram and ethylhexyl nitrate and EEGLs for hydrogen chloride, the subcommittee has identified deficiencies in the data and made recommendations for additional research. The subcommittee believes that the recommended exposure levels will provide adequate protection for workers and soldiers from these chemicals.

Bernard Wagner, *Chairman*
Subcommittee on Permissible Exposure Levels

John Doull, *Chairman*
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Contents

1 Introduction

The possibility of sudden contamination of air during military operations has created the need for guidance regarding emergency exposure of people to chemicals. Regulatory agencies such as the U.S. Environmental Protection Agency and the Occupational Safety and Health Administration are concerned with air pollutants—such as oxides of nitrogen and sulfur, oxidants, hydrocarbons, and carbon monoxide—for which community and workplace environmental-exposure standards are set. However, their interests do not include short-term, unpredicted exposures to chemicals that might be encountered in military operations or exposures to chemicals used primarily by the armed forces. During the past several years, the U.S. Army, the U.S. Air Force, and the U.S. Navy have requested that the National Research Council's Committee on Toxicology (COT) recommend short-term exposure levels for a large number of chemicals of interest. COT has developed guidance levels for 41 of these substances (NRC, 1984a,b,c; 1985a,b; 1986a; 1987; 1988). The basis for establishing these exposure guidance levels also has been described by COT (NRC, 1964, 1971, 1979, 1986b).

This report of the Subcommittee on Permissible Exposure Levels of the Committee on Toxicology was prepared in response to requests by the U.S. Navy and U.S. Army to recommend permissible exposure levels (PELs) for zinc dimethyldithiocarbamate (ziram) and 2-ethylhexyl nitrate and 2-min emergency exposure guidance levels (EEGLs) for hydrogen chloride.

The objectives of the subcommittee were as follows:

- To review the toxicity data on ziram, ethylhexyl nitrate, and hydrogen chloride.
- To recommend interim PELs for ziram and ethylhexyl nitrate and 2-min EEGLs for hydrogen chloride.

• To identify data gaps and make recommendations for further research on toxicities of these chemicals so that acceptable exposure levels may be recommended with more confidence by the subcommittee in the future.

EEGLs refer to concentrations of airborne substances (such as gas, vapor, or aerosol) that permit continued performance of specific tasks during rare emergency conditions lasting 1–24 hr. PELs refer to average exposures to airborne substances that are permitted in any 8-hr work shift of a 40-hr work week.

Immediate and delayed health effects are considered in establishing an EEGL or PEL. Immediate effects, although often transitory, might well impede the performance of exposed persons. Immediate effects can also be long-lasting. Delayed effects, slow in onset, can continue for long periods and are difficult to predict from the effects of acute exposures.

It is inappropriate to use EEGLs for planned exposures, because EEGLs are neither safe nor hygienic. Exposure at an EEGL might produce reversible effects that do not impair judgment and do not interfere with proper responses to the emergency (such as shutting off a valve, closing a hatch, removing a source of heat or ignition, or using a fire extinguisher).

"Emergency" connotes a rare and unexpected situation with potential for significant loss of life, property, or mission accomplishment if not controlled. An EEGL is acceptable only in an emergency, when some risks or some discomfort must be endured. Even in an emergency, exposure should be limited to a defined short period. An EEGL is intended to prevent irreversible harm. For example, in normal work situations, a degree of upper respiratory tract irritation or eye irritation causing discomfort would not be considered acceptable; during an emergency, it would be acceptable if it did not cause irreversible harm or affect judgment or performance seriously. The EEGL for a substance represents COT's judgment based on evaluation of experimental and epidemiological data, mechanisms of injury, and operating conditions in which emergency exposure might occur.

However, EEGLs do not represent hard lines between safe and unsafe concentrations. If an EEGL is exceeded, it should be expected that some people will be affected adversely.

The military is encouraged to have appropriate emergency protective equipment readily available, such as air-supplied respirators and

protective clothing. Relevant emergency escape procedures should also be developed, and potential emissions should be monitored.

Exposure at an EEGL is assumed to be a rare experience in a person's lifetime. How often this experience is allowed to take place depends on the chemical substance and its consequences. At a minimum an adversely affected person should have time to recover from the effects fully before re-exposure at the EEGL. EEGLs should help to guide the planning for and response to an emergency rather than be considered part of a normal operation.

In estimating the EEGL or PEL of a substance that has multiple toxic effects, all the adverse effects—including reproductive (in both sexes), developmental, carcinogenic, neurotoxic, respiratory, and other organ-related effects—are evaluated, and the most seriously debilitating, work-limiting, or sensitive effect is selected as the basis for guidance. COT's recommendations are consistent with the prevailing scientific view that a single exposure to a carcinogen can lead to cancer, although the probability of such a consequence may be low.

In the absence of better information, the use of safety factors might be appropriate and is consistent with suggestions made by the NRC's Safe Drinking Water Committee (1986c). If only animal data are available and extrapolation from animals to humans is necessary, a safety factor of 100 is suggested. If the likely route of human exposure differs from that of a relevant experiment, an additional safety factor of 10 is suggested. If the substance under consideration is carcinogenic, a cancer risk assessment is performed with the aim of providing an estimate of exposure in which an excess risk of cancer would not be greater than 1 in 10,000 exposed persons. The excess risk of 1 in 10,000 exposed persons as accepted by the Department of Defense is chosen for use in evaluating military exposures. This excess risk has been suggested by the International Council on Radiation Protection (1985) for nuclear power-plant workers. It is not considered an acceptable risk for the general population.

PELs and EEGLs are not standards or judgments of acceptable risk and must not be so construed; they are COT's best judgment, based on available evidence. As in all reports by NRC, this report contains only advisory information and recommendations.

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2 *Summary of Subcommittee Recommendations*

Table 1 summarizes PELs or EEGLs for zinc dimethyldithiocarbamate (ziram), 2-ethylhexyl nitrate (EHN), and hydrogen chloride (HCl).

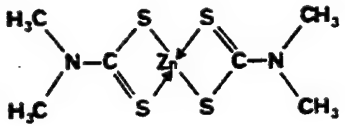
TABLE 1 Recommended Exposure Guidance Levels for Ziram, EHN, and HCl

Substance	Duration of Exposure	Recommendations
Ziram	8 hr/day	0.09 mg/m^3 (PEL)
EHN	8 hr/day	0.05 ppm (PEL)
HCl	2 min (single exposure)	250 ppm (EEGL)
	2 min (repeated exposures)	100 ppm (EEGL)

3 *Zinc Dimethyldithiocarbamate*

BACKGROUND INFORMATION

Physical and Chemical Properties

Chemical structure:	
CAS number:	137-30-4
Modular formula:	$C_6H_{12}N_2S_4ZN$
Molecular weight:	305.82
Chemical name:	Zinc dimethyldithiocarbamate
Synonyms:	Ziram, cuman, corozate, hexazir, zivide
Physical state:	White powder (or crystals)
Melting point:	250°C (crystal); 140°C (dust)
Solubility:	Insoluble in water, slightly soluble in CCl_4 and ethanol
Conversion factors at 25°C, 1 atm:	1 ppm = 12.5 mg/m^3 1 mg/m^3 = 0.08 ppm

Occurrence and Use

Zinc dimethyldithiocarbamate (ziram) is a derivative of dithiocarbamates and is widely used in agriculture as a pesticide and as an antifungal agent. Since 1947, ziram has been used as a liquid fungicide both in the field and on storage crops for the eradication of

fungal infections in rice, potatoes, tomatoes, coffee, fruits, and tobacco. It is registered by the U.S. Environmental Protection Agency for use on 24 fruit and vegetable crops and on several ornamental flowers in the United States. It also has been used in the rubber industry since 1943 as an accelerator in vulcanization. Small amounts are used in industrial fungicides; in combination with other chemicals in preparation of adhesives, paper coatings, and industrial cooling water; in plastics; and in textiles. The U.S. Navy uses ziram as a minor additive in Devoe Coatings Company ABC-3 red and black antifouling coating systems. Ziram is not known to occur as a natural product.

SUMMARY OF TOXICITY INFORMATION

The toxicity or carcinogenicity of ziram has been investigated in a variety of biological systems, and several target tissues such as thyroid and testis have been identified and examined.

Effects on Humans

No case reports or epidemiological studies have been conducted that would provide a data base for evaluating the potential health effects from the exposure to ziram. One study was conducted to evaluate chromosome and chromatid aberrations in cultured lymphocytes derived from industrial workers handling ziram (Pilinskaya, 1971). The aberrations occurred six times more frequently in the workers than in controls. The induced chromosomal breaks were nonrandom and confined mainly to chromosome 2.

Effects on Animals

Acute Toxicity

The LD_{50} of ziram is strikingly different for different species of animals and for routes of exposure. The LD_{50} for single oral doses of ziram is >1,400 mg/kg of body weight for the rat, rabbit, and mouse (Hodge et al., 1952). Guinea pigs appear to be more susceptible, having an LD_{100} of 150 mg/kg (Hodge et al., 1952), and ziram is lethal for birds at 225 mg/kg (Rasul and Howell, 1974). However, when the

chemical is injected intraperitoneally (i.p.), the LD_{50} is much lower for all species and ranges from 23 to 73 mg/kg. A single or acute oral exposure to ziram at 100 mg/kg in rats, guinea pigs, and rabbits does not appear to be lethal. Table 2 summarizes the acute toxicity data of ziram in experimental animal species.

Central Nervous System Effects

Central nervous system disturbances have been reported following the oral administration of ziram (Hodge et al., 1956; Enomoto et al., 1989). Partial paralysis of the hind legs and the degeneration of sciatic nerves have been observed after ingestion of ziram at 2,000 ppm in the diet (100 mg/kg of body weight) of rats exposed for 78 weeks and killed after 104 weeks (Enomoto et al., 1989). This hind leg abnormality was also reported in rats fed 0.25% ziram in their diet (125 mg/kg of body weight) after 2 months (Hodge et al., 1956). Convulsive seizures in dogs fed ziram at 25 mg/kg of body weight for 1 year also have been reported (IARC, 1976).

Reproductive, Teratogenic, and Embryotoxic Effects

The administration of ziram produced a number of reproductive, teratogenic, and embryotoxic effects in mice, rats, and birds. The lowest dose exhibiting maternal weight loss was 12.5 mg/kg (Giavini et al., 1983). The mean maternal weight in control animals was 108 g compared with 88 g in animals receiving ziram in their diet at 12.5 mg/kg per day. Table 3 shows the types of effect observed, species of test animals, routes of exposure, and concentrations tested that elicited these responses.

Immunological Effects

Allergic contact dermatitis is an immunologically mediated, delayed hypersensitivity of the skin to a specific chemical. The guinea pig is the animal species of choice to evaluate materials for their potential to induce human allergic contact dermatitis. When ziram was tested using solutions of 1% and 5%, a mild to moderate degree of contact dermatitis was produced. Ziram may also cross-react with other

TABLE 2 Acute Toxicity of Ziram in Experimental Animal Species

Dose	Route	Duration	Species	Effect	Reference
225 mg/kg	Oral	1 week	Birds	LD_{100}	Rasul and Howell, 1974
120, 250, 500, 1,000, and 2,000 mg/kg	Diet	2 weeks	Mice	LD_{100} All animals died at two highest concentrations; no deaths at other concentrations	NTP, 1983
125, 250, 500, 1,000, and 2,000 mg/kg	Diet	Single	Rats, mice	All animals died at highest concentration; no deaths at other concentrations	NTP, 1983
250, 625, 1,250, 2,500, and 5,000 mg/kg	Diet	2 weeks	Rats	All animals died at 12,500 ppm and above; 2 rats died at 6,000 ppm	NTP, 1983
1,400 mg/kg	Oral	Single	Rats	LD_{50}	Hodge et al., 1952
73 mg/kg	i.p.	Single	Mice		Hodge et al., 1952
23-33 mg/kg	i.p.	Single	Rats		Hodge et al., 1952
500 mg/kg	Oral	Single	Rats		Fishbein, 1976
30 mg/kg	i.p.	Single	Guinea pigs	Lower limit for dose fatal to all animals	Hodge et al., 1952
50 mg/kg	i.p.	Single	Rabbits		Hodge et al., 1952
150 mg/kg	Oral	Single	Guinea pigs		Hodge et al., 1952
1,020 mg/kg	Oral	Single	Rabbits		Hodge et al., 1952

TABLE 3 Reproductive, Teratogenic, and Embryotoxic Effects of Ziram

Dose	Route	Duration	Species	Effect	Reference
25, 50, and 100 mg/kg	Oral	1-5 days of gestation	Rats	Reduction in live fetuses' mean weight at 50 and 100 mg/kg; no effects on number of implantations or number of live fetuses	Giavini et al., 1983
50 mg/kg	Oral	2 weeks; 6.5 months	Mice	Reduction in number of live births	Giavini et al., 1983
12.5, 25, 50, and 100 mg/kg	Oral	6-15 days of gestation	Rats	Reduced maternal weight gain at all dose levels tested; increase in number of deaths of pregnant females at 100 mg/kg level	Giavini et al., 1983
1.25, 12.5, and 125 mg/kg	Diet	2 years	Rats	Testicular development; atrophic testes seen at two highest concentrations (not dose related)	Hodge et al., 1956
56 mg/kg	Oral	18 months	Birds	Smaller testes as compared with controls	Rasul & Howell, 1974
0.2 mg%* 0.1 mg%	Oral	3 weeks	Mice	Atrophy of seminiferous tubules of testes and an impairment of spermatogenesis; increased incidence of sterility in males	Cilievici et al., 1983
	Diet	2 days	Hens	Stopped egg production at all concentrations tested	Weppelman et al., 1980

*Dose is not converted to milligram per kilogram of body weight because the information on the quantity of material administered is not given in the report of Cilievici et al., 1983.

dithiocarbamates such as ferbam, which may potentiate the response (Matsushita et al., 1977).

Hematological Effects

Long-term feeding (52 weeks) of rats at concentrations >200 ppm in their diet (doses of 10 mg/kg of body weight) caused a significant decrease in hematocrit, hemoglobin, and erythrocyte counts (Enomoto et al., 1989). These authors also reported a decrease in serum calcium levels at 2,000 ppm in the diet (100 mg/kg of body weight) (Enomoto et al., 1989). A 2-year feeding study of rats at doses of ziram up to 6.25 mg/kg produced no hematological effects (Hodge et al., 1956).

Mutagenicity and Chromosomal Effects

The mutagenicity of ziram has been tested (NTP, 1983). Ziram was mutagenic with and without metabolic activation when tested against the base substitution-sensitive *Salmonella typhimurium* strains TA 1535 and TA 100 (Hedenstedt et al., 1979; Seiler, 1973); mutagenicity was questionable when tested against the frameshift-sensitive mutants TA 1538 and TA 98. Thiram, the disulfide equivalent of ziram, is also mutagenic to strains TA 1535 and TA 100 with metabolic activation. One negative result has been reported for ziram mutagenicity in tests against standard strains of *S. typhimurium* (TA 1535, TA 1537, TA 1538, TA 98, and TA 100), with and without metabolic activation (NTP, 1983). Ziram was mutagenic in *S. typhimurium* without exogenous metabolic activation (TA 100) and with rat liver S-9 fractions (TA 98, TA 100, and TA 1535); ziram was not mutagenic for TA 1537 (NTP, 1983) and was weakly positive in the recombination assay in *Bacillus subtilis* (NTP, 1983). Ziram did not induce gene conversion in *Saccharomyces cerevisiae* (NTP, 1983).

Rats exposed orally during the first 5 days of pregnancy to ziram at 100 mg/kg exhibited a significant increase in the number of chromosome aberrations in bone marrow cells (Giavini et al., 1983). Other investigations have reported meiotic chromosomal alterations (presence of trivalent and univalent chromosomes) in mice exposed orally for 3 weeks at concentrations of 0.1 and 0.2 mg% (Cilievici et al., 1983).

Pathology and Carcinogenicity

Ziram and other bis-dithiocarbamates may be goitrogenic in laboratory animals and possibly in humans. In a study of workers engaged in the manufacture of thiram (a similar compound), the thyroid appears to be the primary target organ (reviewed in NTP, 1983). Thyroid enlargement and adenocarcinoma, as well as other abnormalities, have been reported in rats (reviewed in NTP, 1983). However, ziram was not goitrogenic in dogs exposed in their diet for 1 year at 25 mg/kg (Hodge et al., 1956). Exposure of rats at concentrations of 2,000 ppm in their diet (100 mg/kg of body weight) for >8 weeks caused an increased incidence of hypertrophy of the thyroid (Enomoto et al., 1989). No such effect was observed at 200 and 20 ppm (10 and 1 mg/kg of body weight). Rats exposed orally at doses as high as 100 mg/kg daily for 1 month did not show any alterations in organ weights (Hodge et al., 1952, 1956).

The thyroid has been recognized as a target organ for thiocarbamate compounds. The iron analog of ziram, ferbam, has been associated with squamous metaplasia of the thyroid in rats exposed daily to 20 or 52 mg/kg for 80 days.

Table 4 provides a summary of various studies conducted to evaluate the carcinogenicity potential of ziram.

The few studies that have examined the carcinogenicity of ziram have been reviewed by NTP (1983) and IARC (1976). IARC (1976) concluded that the limited data available do not allow an evaluation of the carcinogenicity data. NTP tested ziram because of its high production, industrial and agricultural exposure, possible exposure of the general population via food and agriculture industries, and because the previous carcinogenicity studies were not adequate to allow appropriate evaluation of the carcinogenicity of ziram (NTP, 1983). Short-term studies conducted by NTP included a single-dose study, a 2-week study, and a 13-week study using both rats and mice. The authors reported no compound-related histopathological effects.

NTP's 2-year studies used F344/N rats and B6C3F_1 mice. The test rats were exposed to ziram at 300 or 600 ppm in feed (15 or 30 mg/kg of body weight), and the mice were given a diet with ziram at 600 or 1,200 ppm (40 or 80 mg/kg of body weight). C-cell carcinomas of thyroid occurred at a significantly increased incidence in the high-dose male rats and with a statistically significant dose-related trend (control, 0 of 50; low dose, 2 of 49; high dose, 7 of 49). A dose-related trend that was statistically significant occurred in the combined

TABLE 4 Carcinogenicity Studies of Ziram in Rats and Mice

Dose	Route	Duration	Species	Effect	Reference
70 mg/kg	Gavage	22 months	Rats	Two malignant hepatomas and two fibrosarcomas (control also developed a fibrosarcoma)	IARC, 1976
25, 250, 2,500 mg/kg	Diet	2 years	Rats	Three malignant tumors of pituitary; two thyroid adenomas at highest concentration; hyperplastic thyroid at lowest dose (controls also had tumors); effects probably not related to treatment	IARC, 1976
15 mg/kg	Subcut (implantation)	22 months	Rats	Three tumors (hepatoma, fibrosarcoma, lymphosarcoma of the intestines (control had one fibrosarcoma); no tumors at the site of implantation	IARC, 1976
46.4 mg/kg	Subcut (single injection)	22 months	Rats	No increase in tumor incidence	IARC, 1976
4.6 mg/kg for 3 weeks; then 15 mg/kg for 74 weeks	Gavage	78 weeks	Mice	Tumor incidence not different from controls	IARC, 1976
75 mg/kg	Gavage (sacrificed at 6 months)	20 weeks	Mice	Lung edemas (may differ with strain)	IARC, 1976

15 or 30 mg/kg	Diet	2 years	Rats	C-cell carcinomas of the thyroid in male rats at the high dose; combined incidence of C-cell adenoma or carcinoma increased in male rats; these effects not seen in female rats; C-cell hyperplasia of the thyroid observed in male rats at both concentrations; female rats had significant decrease in incidence of mammary gland fibroadenomas at high dose and a dose-related decrease in adenocarcinomas	NTP, 1983
30 or 60 mg/kg	Diet	2 years	Mice	Incidence of alveolar/bronchiolar adenomas in female mice at high dose significantly increased; dose trend significant; malignant lymphoma incidence increased in female mice at high dose (not significant at $p = 0.05$	NTP, 1983
1, 10, and 100 mg/kg	Diet	78 weeks	Rats	Cystic follicles increased at high dose in female mice; incidence of liver adenomas showed a significant dose-related decrease in female mice; incidence of liver carcinomas significantly decreased in male mice	Enomoto et al., 1989

incidence of C-cell adenomas and carcinomas of the thyroid in the male rats fed ziram. The incidence of C-cell adenomas and C-cell carcinomas was not significantly increased in dosed female rats. C-cell hyperplasia of the thyroid gland was observed in both male and female rats. Thyroglossal duct cysts occurred in both male and female rats. C-cell adenomas or carcinomas were not found in mice of either sex. Neither the rats nor the mice had any ziram-related increases in follicular cell tumors (NTP, 1983).

Administration of ziram, its metabolites, or compounds structurally related to ziram has produced various pulmonary effects in mice. Pathological precancerous changes were reported in the lungs of rats administered ziram orally (dose and duration not specified) (WHO/FAO, 1975). Lung congestion, with patches of bronchopneumonia and emphysema, was observed in rats administered 0.05 ml carbon disulfide (a ziram metabolite) in 0.2 ml olive oil by intramuscular injection daily for 40 to 60 days (NTP, 1983). The incidence of lung tumors was found to increase in $B6C3F_1$ mice in carcinogenesis bioassays of tellurium diethyl dithiocarbamate (NCI, 1979a), sodium diethyl dithiocarbamate (NCI, 1979b), and tetraethyl thiram disulfide (NCI, 1979c)—compounds structurally related to ziram. These compounds have carbon disulfide as a common metabolite (NTP, 1983).

Pulmonary effects of ziram in mice were also seen in the NTP study. The increase in alveolar/bronchiolar adenoma incidence in female mice was statistically significant ($p < 0.05$). The incidence was significantly higher in the high-dose group than in the controls ($p < 0.05$). The increase in incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in female mice was also statistically significant ($p < 0.05$). The incidence of alveolar/bronchiolar adenomas was 10 of 50 (20%) and that of alveolar/bronchiolar adenomas or carcinomas (combined) was 11 of 50 (22%) in high-dose female mice. Life-table analysis for these lung tumors showed only a weak trend ($p = 0.071$), primarily because three of the four control animals with lung tumors died before the end of the study.

Pulmonary adenomatous hyperplasia, consistent with the chronic pulmonary lesions following Sendai virus infection, confirmed by serological tests was observed in more than 30% of the male and female mice in both control and dosed groups. The lesions consisted of alveolar macrophages, increased type II pneumocytes, and areas of squamous metaplasia. The histopathological interpretation of lung microscopic sections clearly differentiates between this hyperplasia and pulmonary alveolar/bronchiolar adenomas or carcinomas (NTP,

1983). All mice in the control and dosed groups that had all three test chemical bioassays showed about the same incidence of pulmonary adenomatous hyperplasia. The female mice administered ziram showed a statistically significant increase in pulmonary tumor incidence. In the high-dose group, 6 of the 26 female mice with adenomatous hyperplasia had pulmonary tumors, whereas 4 of the 24 without the adenomatous hyperplasia had pulmonary tumors. In the low-dose group, only 1 of 27 female mice with adenomatous hyperplasia had a pulmonary tumor.

Hepatocellular carcinomas in high-dose male mice and hepatocellular adenomas in high-dose female mice were observed at statistically significant decreased incidences. Hepatocellular carcinomas occurred in 13 of 49 (27%) control males, 8 of 50 (16%) low-dose males, and 1 of 49 (2%) high-dose males in this study (NTP, 1983).

The incidence of fibroadenomas of the mammary gland decreased ($p < 0.05$) in high-dose female rats; the trend was also negative for adenocarcinomas of the mammary gland. In both cases, the incidences of dosed animals with tumors in the present study fell within the historical incidence ranges for control animals with these tumors both in the laboratory that carried out this bioassay and in the bioassay program of NTP as a whole (NTP, 1983).

The conclusions reached by NTP were that under the conditions of these studies, ziram was carcinogenic for male F344/N rats, causing increased incidences of C-cell carcinomas of the thyroid gland. Ziram was not carcinogenic for either female F344/N rats or male $B6C3F_1$ mice. Increased incidences of alveolar/bronchiolar adenomas or carcinomas occurred in female $B6C3F_1$ mice. However, the interpretation of this increase in lung tumors is complicated by an intercurrent Sendai virus infection, but no correlation was found between the presence of pulmonary tumors and Sendai virus infection in the dosed female mice. A significant decrease in the incidence of mammary fibroadenomas occurred in high-dose female rats, and a significant decrease in the incidence of liver tumors occurred in dosed male and female mice.

Pharmacokinetics

Ziram and similar dithiocarbamates probably are metabolized principally by the liver microsomal mixed function oxidases. Water-soluble metabolites of ziram were found in blood, kidney, liver, ovaries,

spleen, and thyroid 24 hr after exposure. Unchanged ziram can also be found in the feces (reviewed in IARC, 1976).

Ziram has not been shown to accumulate in the tissue even after a 1-year exposure at 25 mg/kg administered in the diet of dogs (Hodge et al., 1956). The known impairment of microsomal drug metabolism by sulfur-containing compounds and, especially, carbon disulfide may be due to the binding of an active form of sulfur to the microsomal and cytochrome P-450 systems. Ziram reduced the in vivo and in vitro activity of several liver microsomal enzymes associated with hepatic drug metabolism; this reduction could enhance the pharmacological effects of other drugs taken simultaneously or already present in the affected individual (Zemaitis and Greene, 1979).

EXPOSURE LIMITS

In 1974, the joint meeting of the Food and Agriculture Organization's Working Party of Experts on Pesticide Residues and the World Health Organization's Expert Committee on Pesticide Residues established an acceptable daily intake for humans of 0-0.005 mg/kg for all dithiocarbamate fungicides, including ziram (WHO/FAO, 1975). In the United States, the allowable residues of ziram range from 0.1 ppm for some nuts to 7.0 ppm for fruits and vegetables. No other regulatory exposure limits have been recommended.

SUBCOMMITTEE CONCLUSIONS AND RECOMMENDATIONS

Although substantial amounts of data from various toxicity tests exist, neither epidemiological data nor animal inhalation toxicity data are available on ziram. In considering the establishment of a permissible exposure level (PEL) for ziram, the subcommittee had major concern regarding the general quality of the existing data base. Due to this limitation, it seems appropriate at this time, to recommend only an interim PEL for the noncarcinogenic effects of ziram.

Although no studies evaluated the toxicity or carcinogenicity of ziram by inhalation, there is evidence that this chemical, at certain concentrations, can be expected to be toxic. Because of the conflicting data and uncertainties in the literature, no PEL can be established based on the carcinogenicity of this chemical. The results of the teratogenicity study by Giavini et al. (1983) indicate that maternal toxicity

is the most sensitive toxic end point. Therefore, it seems appropriate to base the PEL on the results of the teratogenicity study in rats conducted by Giavini et al. (1983). In this study, ziram was administered to pregnant rats by gavage at doses of 0, 12.5, 25, 50, 100 mg/kg of body weight per day on days 6-15 of gestation. Ziram has a low teratogenic potential in that it exerts its teratogenicity only at doses that are lethal to 50% of mothers (100 mg/kg). There was a 16% decrement in maternal weight gain during pregnancy relative to control rats receiving the lowest ziram dose. The absence of a dramatic effect on resorptions or fetal weight, coupled with the significant reduction of maternal weight at higher dose levels, suggests that this weight difference is probably ziram-related in these pregnant females. Therefore, the subcommittee accepted 12.5 mg/kg of body weight per day as the lowest-observed-effect level (LOEL) as a basis for setting the 8-hr PEL.

Dividing 12.5 mg/kg per day by a safety factor of 10 for interspecies differences, a safety factor of 10 for intraspecies differences, and a safety factor of 10 for use of LOEL instead of a no-observed-effect level (NOEL) gives a proposed human exposure level of 0.0125 mg/kg per day. To convert this oral dose to an 8-hr PEL in terms of inhalation exposure to ziram in air, it is assumed that a representative male individual weighs 70 kg and inhales 10 m^3 of air in an 8-hr workday; 100% absorption (a conservative assumption in the absence of data on ziram particle size) is assumed also. Multiplication of 0.0125 mg/kg per day by 70 kg and division by 10 m^3 gives an 8-hr workday PEL of 0.0875 mg/m^3 in air or 87.5 $\mu g/m^3$. Therefore, the subcommittee recommends an interim 8-hr PEL of 87.5 $\mu g/m^3$ (or 0.09 mg/m^3) for ziram.

Because of the lack of any information on concentration or particle size of the airborne ziram, the recommended PEL was based on the assumption that all ziram in inhaled air would be deposited in the lungs and absorbed. The particle size may be large enough that the actual deposition is as little as 10%. Therefore, the subcommittee recognizes that this PEL is conservative. Furthermore, the workers in the immediate exposure area are in protective clothing, which would greatly reduce the health risk of such exposure.

The subcommittee highly recommends that additional studies be conducted to include the following:

- Measurements of concentration, exposure mode, and physical properties of the substances in the specific work area of interest.

- Acute, subchronic, and chronic inhalation studies.
- Lifetime carcinogenicity studies by the inhalation route.
- Examination of the shipyard personal medical file to detect any suggestion of adverse effects on workers' health that could be related to such exposures.
- Further studies to determine ziram toxicity by the inhalation route.
- Further research to determine testicular damage from exposure to ziram.

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4 *2-Ethylhexyl Nitrate*

BACKGROUND INFORMATION

Physical and Chemical Properties

Chemical structure:	$CH_3-(CH_2)_3-CH(C_2H_5)-CH_2-O-NO_2$
Chemical formula:	$C_8H_{17}NO_3$
Molecular weight:	175.2
Chemical name:	2-Ethylhexyl nitrate, Nitric acid, 2-ethylhexyl ester
Synonyms:	"Ethyl" DII-3, DII-3 HiTEC 4103 fuel additive
CAS number:	27247-96-7
Physical state:	Pale yellow liquid, ester odor
Boiling point:	>100°C (decomposes)
Melting point:	<-26°C
Specific gravity:	0.96 at 20°C (H_2O = 1)
Vapor pressure:	0.2 mm Hg at 20°C
Solubility:	Negligible in water
Fire and explosion hazard:	Flammable; when heated above 100°C may undergo a self-accelerating, exothermic reaction
Conversion factors at 25° C, 1 atm:	1 ppm = 7.3 mg/m^3 1 mg/m^3 = 0.137 ppm

Occurrence and Use

2-Ethylhexyl nitrate (EHN) is a flammable liquid used as an additive to increase the cetane number of diesel fuel. Because the compound is an organic nitrate, EHN is likely to be a vasodilator similar to nitroglycerin (Fukuchi, 1981; Ignarro et al., 1981; Zitting and Savolainen, 1982).

SUMMARY OF TOXICITY INFORMATION

Effects on Humans

Persons administered organic nitrates as vasodilators for the treatment of cardiovascular disease develop a tolerance to the compounds (Parker, 1990). Recent work has indicated that the endothelium-derived relaxing factor is NO (Palmer et al., 1987), and organic nitrates relax vascular smooth muscle cells by producing NO via an *s*-nitrothiol pathway (Ignarro et al., 1981). The nitrothiols stimulate guanylate cyclase to form more cyclic guanosine 5'-phosphoric acid (GMP), which results in smooth-muscle relaxation via still undefined mechanisms. Evidence from studies performed in vitro shows that the development of tolerance to organic nitrates may be caused by depletion of sulfhydryl compounds (Kukovetz and Holzmann, 1990). The development of tolerance in strips of smooth muscle treated with nitroglycerin in vitro is prevented by addition of cysteine or cysteine-generating compounds (Kukovetz and Holzmann, 1990). The development of tolerance is dose-dependent, occurring at high doses (50-60 mg, three times daily) and, to only a small extent, at low doses (20 mg, three times daily) (Tauchert et al., 1984). Therefore, tolerance would not be expected to develop during low-level incidental occupational exposures.

Exxon reported that one employee complained of nausea, heart palpitation, and weakness while working with EHN in a laboratory hood and presumably exposed to concentrations well below DuPont's recommended acceptable exposure limit (AEL) of 5 ppm, 8-hr time-weighted average (TWA) (C.F. Reinhardt, personal communication, 1989). Exxon also reported that their European affiliate had reported severe headaches and fatigue, in addition to the symptoms noted above, in their workers. These effects were presumably also

experienced at exposure levels below the DuPont AEL of 5 ppm, 8-hr TWA (C.F. Reinhardt, personal communication, 1989).

The Department of Industrial Hygiene and Toxicology of the Institute of Occupational Health in Helsinki reported that workers in the chemical factory in which EHN was diluted with simple aliphatic alcohols reported throbbing headaches. EHN vapors were detected in the workroom area at a level of 5 to 20 ppm (Someroja and Savolainen, 1983).

The Ethyl Corporation, in its "Material Safety Sheet for EHN," states that overexposure to organic nitrates by inhalation of the vapor or by skin contact may cause headache, dizziness, nausea, and decreased blood pressure.

DuPont has reported no illness in its workers handling EHN in 6 years of manufacturing experience. The workers wear full protective clothing (but not respirators) and neoprene or nitrile rubber gloves. Monitoring in the workplace indicates average concentrations of EHN at 0.1 to 0.5 ppm (C.F. Reinhardt, personal communication, 1990).

G. Kennedy, of DuPont, reported that, in general, workers complain of symptoms related to vasodilation if atmospheric concentrations of EHN reach as high as 2 ppm in the workplace (G. Kennedy, personal communication, 1990). Dr. Kennedy also described a limited study in which hypertensive rats were given intra-arterial injections of nitroglycerin, EHN, or propylene glycol dinitrate. All three compounds were approximately equally effective in lowering the blood pressure of the rats, indicating that the three compounds have approximately equal potencies as vasodilators.

Effects on Animals

Acute Toxicity

Oral. Following a dose-range finding study, five female and five male rats were administered oral doses of EHN at 10 ml/kg of body weight. After 14 days of observation, three animals (two male, one female) were dead. The oral LD_{50} in rats was calculated to be >9,640 mg/kg; no other toxic signs were noted (Ethyl Corp., C-2475, unpublished document, 1982).

Inhalation. Ten nonfasted female Sprague-Dawley rats weighing 236-273 g were exposed to EHN in a 0.5 m^3 volume stainless steel inhalation chamber. Air flow was 148 L of air per minute. Vapor was generated by heating the test article in a glass flask while bubbling nitrogen through the liquid. The concentration of EHN in the chamber was calculated by determining weight of compound used and dividing by total air flow through the chamber during the test (1,135 g initial weight, 1,084 g final weight). At stated air flow, 15 min is required for equilibrium. Total exposure time was thus 75 min to allow a 1-hr exposure at equilibrium concentration. Animals were observed at 24 and 48 hr for mortality. No deaths were observed within 48 hr of exposure at a concentration of 4.6 mg of EHN per liter of air (Ethyl Corp., C-2475). The 1-hr LC_{50} was calculated to be greater than 4.6 mg/L.

Dermal. Four young adult albino rabbits had abdomens clipped of hair. The area of exposure was then abraded. A dose of EHN at 5 ml/kg was applied to the abraded site, and the trunks were wrapped with a rubber dam. After 24 hr of exposure, the exposed area was sponged off with water. No toxic signs or deaths were observed for 14 days (Ethyl Corp., C-2475). The dermal LD_{50} was calculated to be >4,820 mg/kg (Ethyl Corp., C-2475).

Rabbit Skin Irritation

The DOT patch-test technique was used on the intact skin of female New Zealand White rabbits. Each rabbit received a dose of 0.5 ml under a gauze dressing, and the trunk was wrapped with rubber dam for a 4-hr exposure period. After initial reading, the site was washed with soap and water to prevent further exposure. Skin readings were made again at 48 hr. No corrosion was reported (Ethyl Corp., C-2475).

Rabbit Eye Irritation

Six young adult albino rabbits were used. The right eye of each was treated with 0.1 ml of EHN. Treated eyes were not washed. Readings

were made at 24, 48 and 72 hr. All irritation scores were zero at all readings in all animals (Ethyl Corp., C-2475).

Guinea Pig Sensitization

Irritation Screening Study. EHN was applied undiluted at concentrations of 25%, 50%, and 75% (wt/vol) in mineral oil to the skin of four guinea pigs. Test sites were occluded for 24 hr. Irritation was evaluated at 24 and 48 hr after removal of the bandages. EHN did not cause erythema or edema at any of the test sites. Undiluted material was used for the induction phase, and a 50% (wt/vol) mixture was used for the challenge (Ethyl Corp., C-2475).

Definitive Test. Twenty guinea pigs (Dunkin Hartley strain) were assigned to both the test and the naive-control group and 10 animals to both the positive-control (sulfathiazole) and the naive-positive-control group. On day 1, test and positive-control animals received injections of Freund's adjuvant, 5% (wt/vol) test or positive-control materials in sterile water, and 5% (wt/vol) test or positive-control material in Freund's adjuvant mixture on the shoulder region. Six days later, animals receiving test- or positive-control material were pretreated with sodium lauryl sulfate applied topically at the injection site. On day 7, undiluted EHN or positive-control material was applied to the injection site and occluded for 48 hr. Fourteen days after the topical application, all animals received a challenge dose on the right flank. Undiluted EHN was applied to test and naive animals. Sulfathiazole was applied to positive-control animals. All test sites were occluded for 24 hr and then wiped clean. Test sites were examined for erythema and edema at 24 and 48 hr after patch removal.

None of the test, naive, or positive-naive animals exhibited a dermal reaction to the challenge application. All of the positive-control animals exhibited dermal reactions. Thus, EHN did not cause a sensitization reaction.

Subchronic Inhalation Toxicity

In a 2-week inhalation study at Haskell Laboratory of DuPont, rats were exposed to EHN at 14, 42, or 140 ppm (Haskell Laboratory, MR-

2713-28, HL 466-82, MR-4613-1, MR-7012-1, HL 421-85, unpublished documents). No clinical signs of toxicity were observed. Body weight was reduced at 140 ppm. Increased relative liver and spleen weights were found at 42 and 140 ppm. Histologically, effects were found in the liver and kidneys at all test levels. Exposure-related histopathological changes included eosinophilic cytoplasmic inclusions in cells of the renal proximal tubules and lipid-like cytoplasmic hepatocellular vacuolation. Both hepatic and renal changes were considered to be slight degenerative changes and recovery was almost complete after a 14-day recovery period. These changes were thought to be related to fasting. To determine if they were compound related, a second study was conducted at 4.2, 42, and 420 ppm. At 420 ppm, decreased body weight and increased relative liver weight were seen. No effects were seen at 4.2 or 42 ppm. Histopathology showed liver and kidney changes, similar to those seen in the first study, in both controls and test animals. The pathologist's conclusion was that these changes were produced by fasting the rats for 6 or 12 hr and were not compound related. Based on the no-observed-effect level (NOEL) of 42 ppm determined in the second subchronic inhalation study, a limit of 5 ppm (8-hr TWA) was proposed.

Subchronic Dermal Exposure in Rabbits

Dermal exposure to EHN at 50 and 500 mg/kg in six albino rabbits per sex per dose was done for 21 days. Three animals in each group had the skin sites on their trunks abraded, and three had intact skin sites. EHN was applied to skin under gauze pads, and the trunks were occluded with Saran wrap held in place with an elastic bandage. After the 6-hr exposure, sites were gently wiped with corn oil. Elizabethan collars were worn for the 21-day period (Ethyl Corp., C-2475).

Hematology, blood chemistries, body weights, organ weights, and food consumptions were measured. Histopathological examination was performed on treated and untreated skin, all gross lesions, heart, trachea, lungs, spleen, liver, gastrointestinal tract (stomach, mesentery, small and large intestine, and cecum), kidney, bladder, testis or ovary, adrenal, thyroid, and brain. Clinical pathology included albumin, globulin, a/g ratio, alkaline phosphatase, direct and indirect bilirubin, blood urea nitrogen, creatinine, gamma globulin transaminase, glucose, serum iron, lactate dehydrogenase, magnesium, phosphorus, total protein, potassium, serum glutamic-oxaloacetic transaminase, serum

glutamic-pyruvic transaminase, sodium, triglycerides, and uric acid. Initial and final values of blood chemistry and hematology were compared. No clear dose-related effects were seen on any of these parameters.

Neurochemical Effects in Rats

A group in the Department of Industrial Hygiene and Toxicology of the Institute of Occupational Health in Helsinki reported a study to determine neurochemical effects of EHN (Someroja and Savolainen, 1983). Rats were injected intraperitoneally (i.p.) with a single dose of EHN at 100 mg/kg of body weight. A small percent of the dose (0.3%) was excreted in the urine within 24 hr. No urinary nitrite was found within the first 5 hr of injection, but an hourly output of nitrate of 26.9 ± 15.8 mg/kg was detected between 5 and 24 hr. Cerebral glutathione concentration was below the control level after 1 day, but returned to control values 3 to 7 days after EHN administration. Brain acetylcholinesterase activity was marginally decreased after 1 day, and RNA content and succinate dehydrogenase activity were normal. The authors concluded that the pharmacological mechanism of action of EHN was probably similar to that of nitroglycerin, i.e., relaxation of the smooth muscle in the blood vessel wall. The authors suggested that EHN might be more potent than nitroglycerin in view of its considerable clinical effects in exposed workers. However, they noted that the biochemical studies indicated no major structural damage caused by this larger dose of EHN. Thus, they concluded that the clinical symptoms experienced by exposed workers may be largely functional but may be sufficiently disabling to necessitate strict control of exposure to the substance.

Mutagenicity and Related Tests

EHN was tested for its mutagenicity in Ames mutagenicity assay. Tester strains used were *S. typhimurium* TA 1535, TA 100, TA 1537, TA 1538, and TA 98. The test compound did not induce a significant increase in the number of revertant colonies. Presence of an exogenous source of liver enzymes did not affect the mutagenicity of the test agent (Ethyl Corp., C-2475).

An in vitro mammalian cell transformation assay with BALB/3T3 clone A31 mouse cells was performed according to the methods of Kakunaga (1973) and Schechtman and Kouri (1977). The positive control chemical was *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG). A stock solution of EHN was prepared in dimethylsulfoxide (DMSO) (Ethyl Corp., C-2475). EHN exposure produced one type III focus (transformation frequency rate of 0.11×10^{-4}). No other type III foci were seen with the other concentrations of EHN. The positive control (MNNG) induced seven morphologically transformed foci (transformation frequency of 2.2×10^{-4}). The negative control (DMSO, 0.25%) produced no spontaneous transformants. The authors concluded that EHN did not induce statistically significant transformations in BALB/3T3 cells.

Pharmacokinetics

Little pharmacokinetic information on EHN is available. The work by Someroja and Savolainen (1983) indicated that very little of the EHN that was injected i.p. into rats was excreted as the parent compound in the urine within 24 hr. However, pharmacokinetic information is available on other organic nitrates used for medical purposes, and there is no reason to think that EHN would behave differently. All medically used organic nitrates are rapidly metabolized and eliminated from the body (Grobecker, 1990). The longest duration of action of any of the compounds is associated with isosorbide-5-mononitrate, which is reported to have a half-life of 4-6 hr. Thus, one would not expect accumulation of the parent compound in the body with intermittent exposures.

There are no reports of the metabolites formed from EHN itself, but studies on other organic nitrates suggest that the compound will be metabolized by nitrate reductase and glutathione-S-transferase to form an alcohol derivative and nitrate ion (Grobecker, 1990). The latter forms the active agent for vasodilation. In the case of EHN, the alcohol formed is 2-ethylhexanol, which can be oxidized to 2-ethylhexanoic acid, a known teratogen (Hanck et al., 1990). The same compound is formed from the plasticizer di-(2-ethylhexyl)phthalate, which is metabolized to form 2-ethylhexanol and, ultimately, 2-ethylhexanoic acid. This compound is believed to be the proximate teratogen responsible for the teratogenic effects of the plasticizer (Ritter et al., 1987).

INHALATION EXPOSURE LIMITS

No recommendations for exposure to EHN have been made by the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH). In the past, DuPont recommended an acceptable exposure limit (AEL) of 5 ppm, 8-hr TWA, based on their studies, which indicated a no-effect level of exposure of rats to EHN at 42 ppm for 6 hr each day, 5 days a week for 2 weeks. DuPont is planning to lower those limits (G. Kennedy, personal communication, 1990). The new limits will be determined upon completion of appropriate toxicology studies. The Ethyl Corporation lists a recommended AEL of 10 ppm, 8-hr TWA, in its "Material Safety Data Sheet." The Navy, in the absence of other guidance, has recommended that the AELs for Otto Fuel II be followed (U.S Navy, 1990). Seventy-five percent of this fuel is the organic nitrate propylene glycol dinitrate. The PEL, 8-hr TWA for this compound is 0.05 ppm and the short-term exposure limit (STEL) is 0.2 ppm (15-min sampling period). The STEL for another organic nitrate, nitroglycerin, is 0.01 ppm, and the ACGIH threshold limit value (TLV) for nitroglycerin is 0.05 ppm, 8-hr TWA.

SUBCOMMITTEE CONCLUSIONS AND RECOMMENDATIONS

EHN is a compound that has low acute toxicity according to animal studies. No chronic toxicity studies have been conducted. The longest exposure studies reported were a 14-day inhalation exposure in rats and a 21-day dermal exposure in rabbits. Based on the negative mutagenicity data and cell transformation assays, testing for carcinogenicity of this compound would have low priority.

Despite the negative animal data, anecdotal information from humans exposed occupationally indicate that exposures to 5 ppm EHN and lower concentrations can cause temporary but disabling headaches and symptoms consistent with lowered blood pressure. Therefore, EHN always should be handled in an enclosed process and never in the open air. Workers should wear protective clothing to minimize dermal exposures, and if the PEL or STEL is likely to be exceeded, appropriate respiratory protection must be worn. Based on current information, the highest concentration of EHN that is reported to be tolerated well by workers is 0.5 ppm (C.F. Reinhardt, personal communication, 1990). Therefore, the subcommittee recommends that the

STEL for EHN be 0.5 ppm until additional information is available. In recognition that some members of the work force may be more sensitive to organic nitrates than others, the subcommittee recommends that the PEL, 8-hr TWA should be 1/10th that value, or 0.05 ppm. This recommendation is in line with other current regulations for other organic nitrates.

Because 2-ethylhexanoic acid (a metabolite of EHN) is teratogenic in animals, EHN itself also may be teratogenic in animals. In the absence of any information defining the level of exposure required for that toxic effect, the subcommittee cannot define a safe level of exposure for women of childbearing age. The subcommittee recommends that developmental toxicity studies be conducted on EHN to determine its potential to cause such toxicity and to establish a NOEL.

Studies in animals or limited studies in humans are an important research need to determine the dose (concentration × time)-response relationship of EHN for the lowering of blood pressure and, in humans, the induction of headaches. Further studies should be conducted to determine the teratogenic potential of EHN.

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5 *Hydrogen Chloride*

BACKGROUND INFORMATION

Physical and Chemical Properties

CAS number:	7647-01-0
Molecular formula:	HCl
Molecular weight:	36.47
Vapor density:	1.26
Solubility:	Highly soluble in water forming hydrochloric acid
Odor:	Pungent
Odor threshold:	1-5 ppm
Conversion factors at 25° C, 1 atm:	1 ppm = 1.49 mg/m^3 1 mg/m^3 = 0.67 ppm

SUMMARY OF TOXICITY INFORMATION

Effects on Humans

The National Research Council (NRC, 1987) reviewed the toxicological effects of hydrogen chloride (HCl) in humans. The report concluded that exposure to irritating concentrations of HCl may result in coughing, pain, inflammation, edema, and desquamation in the upper respiratory tract. Acute exposure to high concentrations may produce constriction of the larynx and bronchi, and closure of the glottis. Much of the literature on human effects of HCl contains qualitative observations, and some uncertainties exist pertaining to analytical methods and precise concentrations. Table 5 summarizes the human data.

TABLE 5 Summary of Toxic Effects of Human Exposure to HCl

HCl Concentration, ppm	Exposure Time	Effects	Reference
1,000-2,000	"Brief"	"Dangerous for even short exposures"*	Henderson and Haggard, 1943
50-100	1 hr	Tolerable	Henderson and Haggard, 1943
10-50	Few hours	Maximal tolerable concentration	Henderson and Haggard, 1943
35	—	Irritation of throat after short exposure	Henderson and Haggard, 1943
10	Prolonged	No adverse effects	Henderson and Haggard, 1943
1-5	—	Odor threshold	Heyroth, 1963

*It is an opinion of Henderson and Haggard (1943) based on earlier work in which humans were exposed to lower concentrations.

Source: NRC, 1987.

Effects on Animals

Acute Toxicity

Groups of two to four guinea pigs conditioned to exercise received whole-body exposure while running in air containing HCl at 107, 140, 162, or 586 ppm (Malek and Alarie, 1989). Exposures lasted for 30 min or until the guinea pigs were incapacitated, i.e., could no longer run and did not resume running. Animals exposed to HCl at 107 ppm completed the running protocol of 30 min, while the other groups were incapacitated after an average of 16 min (140 ppm), 1.3 min (162 ppm), and 0.6 min (586 ppm). The low-exposure group exhibited signs of mild irritation, while the other groups showed signs of severe irritation and coughing and gasping prior to incapacitation. Respiratory frequency was decreased an average of 80% from sedentary baseline values in incapacitated animals. All animals in the highest ex-

posure group died within an average of 3 min from the start of exposure. No deaths occurred in any other group, although the animals may have been observed only briefly following exposure, and any delayed effects would not have been detected. Gross pathological examinations revealed no indications of obstructed nostrils, hyperinflated lungs, or external lung hemorrhage. Histopathological examinations were not conducted. In the absence of pathological changes, the authors concluded that deaths may have resulted from enhanced protective respiratory reflexes due to exercise, resulting in increased toxicity of HCl compared with sedentary exposures.

In another study, groups of four to eight guinea pigs were exposed to HCl at 320, 680, 1,040, or 1,380 ppm for 30 min (Burleigh-Flayer et al., 1985). A decrease in respiratory rate and a lengthened expiratory phase were interpreted as signs of sensory irritation, while an initial increase in respiratory rate followed by a decrease due to a pause following each expiration was interpreted as a sign of respiratory irritation. Two of eight animals died during exposure at 1,380 ppm. One animal in the 1,380-ppm exposure group and two of eight in the 1,040-ppm exposure group died following exposure. Corneal opacities were observed in all five of the surviving animals in the 1,380-ppm group, in four of six in the 1,040-ppm group, and in one of four in the 680-ppm group. Following exposures, pulmonary function was evaluated at various intervals up to 15 days by exposing the animals to room air followed by challenge with 10% CO_2. The authors concluded that tidal volumes during exposure to both room air and CO_2 challenge were unaffected by HCl. However, marked decreases in respiratory rates from pre-exposure baselines were observed in the two highest exposure groups exposed to either room air or 10% CO_2. These changes persisted throughout the 15-day observation period. No changes occurred in lung weights relative to body weights in any exposure group. Histopathological examination of the lungs from the group exposed to HCl at 1,040 ppm revealed inflammatory changes, including alveolitis with congestion and hemorrhage 2 days following exposure, and inflammation, hyperplasia, and mild bronchitis 15 days following exposure. No other groups were examined.

Single baboons were exposed to HCl at 190, 810, 890, 2,780, 11,400, 16,570, or 17,290 ppm for 5 min (Kaplan, 1987). The animals had been conditioned to an escape-performance test, which was begun after the 5-min exposure. An increase occurred in the number of attempts to escape after exposure compared with baseline values before exposure, indicating an irritative response in the animals. Other

signs of irritation were coughing and frothing at the mouth at 810 ppm, progressing to profuse salivation, blinking and rubbing the eyes, and head-shaking at higher concentrations. The animals exposed at 16,570 and 17,290 ppm exhibited severe dyspnea that persisted after exposure, followed by death several weeks later from bacterial infections. Histopathological examination of those animals revealed pneumonia, pulmonary edema, and tracheitis with epithelial erosion.

Groups of three male baboons were exposed under ketamine anesthesia to target concentrations of HCl at 500, 5,000, or 10,000 ppm for 15 min (Kaplan et al., 1988). Analytical data indicated that actual exposures were within 20% of target concentrations in all experiments except one in which the difference was approximately 30%. Respiratory rates during exposures increased in a dose-related fashion: approximately 30%, 50%, and 100% at the three levels compared with baseline rates. Tidal volumes were unaffected by HCl exposure. PaO_2 (arterial blood gas) decreased approximately 40% within the 15-min exposure at the two highest exposures, but not at 500 ppm, and remained lower at least 10 min following exposures before returning to baseline by the time the next analysis was done on day 3. Pulmonary function tests conducted 3 days and 3 months following exposures did not reveal changes relative to baseline values. The responses of animals challenged on day 3 with 10% CO_2 were no different from those before HCl exposure. However, respiratory frequency seemed to increase following CO_2 challenge 3 months after HCl exposure in the two highest exposure groups but not in the 500-ppm group.

A group of mice was exposed to HCl at 309 ppm (RD_{50}, the concentration reported to reduce the respiration rate by 50%) for 6 hr per day (Buckley et al., 1984). After three exposures, all the mice had either died or were moribund, and exposures were discontinued. Histopathological examination revealed severe exfoliation, erosion, ulceration, and necrosis of the nasal respiratory epithelium, but only slight to mild changes in the squamous epithelium and olfactory epithelium. No changes were observed in the lower respiratory tract.

Groups of three Sprague-Dawley rats were exposed to HCl at 200, 295, 784, 1,006, or 1,538 ppm for 30 min (Hartzell et al., 1985). During exposure, respiratory frequency declined in an exposure-related fashion and appeared to reach its maximum decrease within 2 min of the start of exposure to each concentration. Respiratory minute volume decreased similarly, and thus the tidal volume was not substantially altered. Respiratory frequency appeared to be a linear function

of log HCl concentration. The concentration of HCl associated with a 50% decrease in respiratory frequency (RD_{50}) was 560 ppm.

The 5-min LC_{50} of HCl for Wistar rats was approximately 41,000 ppm, and for mice, approximately 13,745 ppm (DiPasquale and Davis, 1971). Exposed animals exhibited pulmonary edema of varying degrees of severity, and pulmonary hemorrhage was observed at lethal concentrations. No other details were given.

Groups of Swiss-Webster mice were exposed to concentrations of HCl ranging from 201 to 20,000 ppm for 10 min (Barrow et al., 1979). Sensory irritation, indicated by a decrease in frequency of respirations, was observed at concentrations >50 ppm. Two of four mice exposed at 8,000 ppm, and four of four mice exposed at 19,300 ppm died. Ocular damage indicated by polymorphonuclear leukocyte infiltration of the conjunctiva was observed in animals exposed to HCl at 480 ppm, corneal necrosis was observed at 700 ppm, and severe damage to the globes was observed at 3,000 ppm. Histopathological examination revealed ulceration in the nasal epithelium in animals exposed at 120 ppm, damage to nasal skeletal structures with necrosis at 700 ppm, and complete destruction of naso- and maxilloturbinate bones at 7,000 ppm.

Groups of 10 Sprague-Dawley rats and 10 ICR mice were exposed to either HCl vapor or aerosol for 5 or 30 min to compare toxicity of each form of the compound (Darmer et al., 1974). Analysis of the aerosols indicated that no droplets were larger than 5 mm in diameter. Animals were observed for 7 days following exposure. The LC_{50}s are shown in Table 6.

TABLE 6 LC_{50}s of HCl Vapor and Aerosol in Rats and Mice*

	5-Min LC_{50} (ppm)		30-Min LC_{50} (ppm)	
Animal	Gas	Aerosol	Gas	Aerosol
Rats	41,000	31,000	4,700	5,600
Mice	13,700	11,200	2,600	2,100

*Data from Darmer et al., 1974.

Gross pathological examination of animals that died during exposure revealed moderate to severe changes in lungs and upper respiratory tract. Animals surviving 7 days following exposure showed pulmonary effects, including indications of alveolar damage. Unspecified histopathological changes were also observed. The authors concluded that the toxicities of HCl vapor and aerosol were similar.

Table 7 summarizes the acute toxicity data of HCl in experimental animals.

Subchronic and Chronic Toxicities and Carcinogenicity

The NRC (1987) reviewed the data from repeated exposures of experimental animals to HCl and concluded that the primary effect was upper respiratory irritation. Rats and mice were exposed to HCl at 10, 20, or 50 ppm for 6 hr per day, 5 days per week for 90 days (Toxigenics, 1984). Histopathological examination revealed minimal to mild rhinitis in exposed rats, and cheilitis and very mild degenerative changes in the nasal turbinates of all exposed mice. The degenerative changes were typical of those seen following exposure to many irritants and are considered reversible following cessation of exposure. Rats receiving lifetime exposure at 10 ppm for 6 hr per day, 5 days per week developed a higher incidence of laryngeal and tracheal hyperplasia than controls did but showed no evidence of HCl-induced tumors (Sellakumar et al., 1985).

Developmental and Reproductive Toxicities

Rats received a single 1-hr exposure to HCl at 300 ppm either 12 days before mating or on day 9 of pregnancy (Pavlova, 1976). Embryo/fetal toxicity was observed, which appeared to be secondary to severe maternal pulmonary effects.

EVALUATION OF TOXICITY INFORMATION

HCl is a potentially severe respiratory tract irritant in humans. However, the irritating properties of HCl prevent more than transient voluntary exposure to concentrations that are likely to cause serious adverse effects. Thus, the paucity of quantitative human data makes

it difficult to evaluate the health effects of exposure to high levels of HCl or to develop guidelines for short-term exposure limits such as an emergency exposure guidance level (EEGL).

Extrapolation of data derived from rodent models has been used to establish short-term exposure guidelines for HCl and to gain a perspective on the mechanisms and effects of high-level acute exposures in humans. The NRC (1987) derived a 10-min EEGL for HCl by applying a three-fold safety factor to the 10-min RD_{50} in mice. Based largely on data in mice, it was assumed that this concentration would cause significant irritation, that histopathological effects might be seen in mice at exposures near the RD_{50}, and that higher exposures would result in significant persistent injuries to the respiratory tract.

Following exposure to high concentrations of HCl, rodents exhibit signs of both sensory and respiratory irritation. Sensory irritation is evoked by stimulation of trigeminal nerve endings in the nasal passages, whereas respiratory irritation occurs through contact of HCl with the lower respiratory tract. As HCl is inhaled, the highly soluble gas (or mist) readily dissolves in the mucosal lining of the nasal passages. When the "scrubbing" mechanism is overwhelmed at high concentrations, HCl enters the lower respiratory tract. Thus, at a given concentration, a delay occurs between the onset of signs of sensory irritation and signs of respiratory irritation. In rodents, each type of irritation shows specific thresholds and dose-response curves. Each type of irritation can be detected by monitoring respiratory patterns.

Recent studies have demonstrated significant differences in responses to HCl exposure between primates and rodents. Exposure of rodents to HCl produces dose-related decreases in respiratory frequency and increases in pauses between breaths, changes that are interpreted as protective mechanisms. Baboons exposed to concentrations of up to 17,000 ppm for 5 min, however, exhibited increases in respiratory frequency that could be interpreted as a compensatory mechanism in response to hypoxia. Moreover, conditioned baboons were able to perform tasks at these high concentrations. Although levels above 11,000 ppm produced delayed deaths, concentrations up to 500 ppm did not produce permanent respiratory function damage.

The data indicate that lethality sometimes occurred in rodents following moderately high HCl exposures without obvious histopathological causes. Based on these data, it is possible that protective respiratory mechanisms, in rodents, which were exacerbated by exercise, were the proximate cause of lethality among the test animals acutely exposed to moderately high HCl concentrations. This view is

TABLE 7 Acute Toxicity Studies of HCl in Experimental Animals

Species	Regimen	Results and Comments	Reference
Mice	Acute LC_{50} determination	5-min LC_{50}: 13,745 ppm. Pulmonary edema at lower doses to pulmonary hemorrhage at lethal concentrations.	DiPasquale and Davis, 1971
Mice, Swiss-Webster	20-20,000 ppm, 10-min exposures	Sensory irritation (decreased respiratory frequency) at >50 ppm. Lethality at 8,000 (2/4) and 19,300 (4/4) ppm. Ocular damage ≥480 ppm. Damage to nasal epithelium: ulceration at 120 ppm to complete destruction of bone at 7,000 ppm.	Barrow et al., 1979
Mice	309 ppm (RD_{50}) 6 hr day	All mice died or were moribund by third exposure. Severe irritation of nasal respiratory epithelium; slight to moderate changes in olfactory epithelium; no changes in lower respiratory tract.	Buckley et al., 1984
Rats, Wistar	Acute LC_{50} determination	5-min LC_{50}: 41,000 ppm. Pulmonary edema at lower doses to pulmonary hemorrhage at lethal concentrations.	DiPasquale and Davis, 1971
Rats, mice, 10/group	Gas or aerosol, 5- and 30-min exposures	LC_{50}s were not significantly different for two forms. LC_{50}s (aver.): rats—36,000 ppm, mice—12,500 ppm at 5 min; rats—5,200 ppm, mice—2,400 ppm at 30 min.	Darmer et al., 1974
Rats, Sprague-Dawley	200, 295, 784, 1,006, 1,538 ppm, 30-min exposures	Exposure-related decrease in respiratory frequency and minute volume; maximum effect within 2 min of start of exposure. RD_{50} was 560 ppm.	Hartzell et al., 1985

Guinea pigs, 4-8/group	320, 680, 1,040, 1,380 ppm, 30-min exposures	Authors differentiate between sensory and respiratory irritation. Deaths were 2/8 at 1,380 ppm during exposure, 1/8 at 1,380 ppm and 2/8 at 1,040 ppm following exposures. Corneal opacity: 0/4, 1/4, 4/6, and 5/5 in exposed groups. Marked decrease in respiratory rates at 1,040 and 1,380 ppm on challenge with CO_2 postexposure, but tidal volumes not affected.	Burleigh-Flayer et al., 1985
Guinea pigs, 2-4/group	107, 11140, 162, 586 ppm, 30-min exposures	Guinea pigs acclimatized to exercise (running) device. Average performances for 30-min exposures were: 107 ppm—all completed 30 min, 140 ppm—16 min, 162 ppm—1.3 min, 586 ppm—0.6 min. Mild to severe irritation (≥140 ppm); cough, gasping (≥140). Deaths within 3 min at 586 ppm. Decreased respiratory frequency (by 80%) in incapacitated animals.	Malek and Alarie, 1989
Baboons, 1 at each level	190, 810, 890, 2,780, 11,400, 16,750, 17,290 ppm, 5-min exposures	Baboons conditioned to escape performance test. Exposure-related increase in escape attempts following exposures. Cough, frothing at mouth at 810 ppm progressing to signs of severe irritation at higher concentrations. Delayed death in animals at 16,750 and 17,290 ppm.	Kaplan, 1987
Baboons, 3/group	500, 5,000, 10,000 ppm, anesthetized, 15-min exposures	Exposure-related increases in respiratory rates; tidal volumes unaffected. PaO_2 decreased at 5,000 and 10,000 ppm. Possible long-term effects in baboons at 5,000 and 10,000 ppm. 500 ppm was NOAEL for effects studied.	Kaplan et al., 1988

supported by the observations that while significant histopathological effects were observed in the nasal passages of rodents following HCl exposures, no effects were observed in the lower respiratory tracts except at high exposures. In addition, mice appear to be much more susceptible to the lethal effects of HCl than other rodents or baboons. To some extent, this increased susceptibility may be due to less effective scrubbing of HCl in the upper respiratory tract. The data suggest that the effects on mice of acute exposure to HCl may not be an appropriate model for extrapolation to humans.

INHALATION EXPOSURE LIMITS

Table 8 lists inhalation exposure limits for HCl recommended by various organizations, which is further incorporated in Figure 1 for easy reference.

SUBCOMMITTEE CONCLUSIONS AND RECOMMENDATIONS

Mice appear more sensitive to HCl exposure than other rodents tested, and rodents in general appear to respond differently from baboons to HCl exposure. Given the greater similarity in the respiratory tract and its function to humans, it appears reasonable that baboons would be a more appropriate animal model for extrapolation of HCl effects to humans. Baboons exhibited irritation during a 5-min exposure to HCl at 810 ppm, but not at 190 ppm, which would be considered the no-observed-adverse-effect level (NOAEL). Baboons exposed at 500 ppm for 15 min also exhibited signs of irritation, based on increased respiratory rates, but did not develop hypoxia, did not show changes in respiratory function, and were able to perform escape tasks. In addition, guinea pigs exposed at 680 ppm for 30 min did not show changes in pulmonary function. It appears from these data that exposure to HCl for 2 min at levels approaching 500 ppm would not produce permanent injuries, although the effects of sensory irritation on the performance of complex tasks are uncertain at levels around 500 ppm. Therefore, the subcommittee recommends a 2-min EEGL of 250 ppm. This exposure level may produce eye and respiratory tract irritation, but all effects should be reversible, and brief exposure at that level should not impair judgment or interfere with proper responses to an emergency. As the NRC (1987) stated, exposure to this

TABLE 8 Currently Recommended Exposure Levels for HCl

Recommended Level	Concentration, ppm
Emergency Response Planning Guidelines (ERPG)* Level 1, 1 hr	3
ERPG Level 2, 1 hr	20
ERPG Level 3, 1 hr	100
NRC 2-min Emergency Exposure Guidance Level (EEGL)	250
NRC 2-min repeated EEGL	100
NRC 10-min EEGL	100
NRC 24-hr EEGL	20
NRC 1-hr EEGL	20
U.S. Army Ceiling Limits	
5 min	30
60 min	15
ACGIH Threshold Limit Value (TLV), ceiling limit	5
OSHA Permissible Exposure Limit (PEL), ceiling limit	5
NRC Short-Term Public Emergency Guidance Level (SPEGL)	
1 hr	1
24 hr	1
NRC 90-day Continuous Exposure Guidance Level (CEGL)	0.5

*Recommended by the American Industrial Hygiene Association.

level would be acceptable only in an emergency and as a rare occurrence. Clearly, re-exposure at this EEGL should be permitted only in the absence of residual effects from previous exposures. The recommended 2-min EEGL of 250 ppm would not be applicable to a scenario, as described by the U.S. Army (Col. F.J. Erdtmann, personal communication, 1990), in which exposures during multiple weaponry firings might occur six times daily for up to 14 days. In addition, it

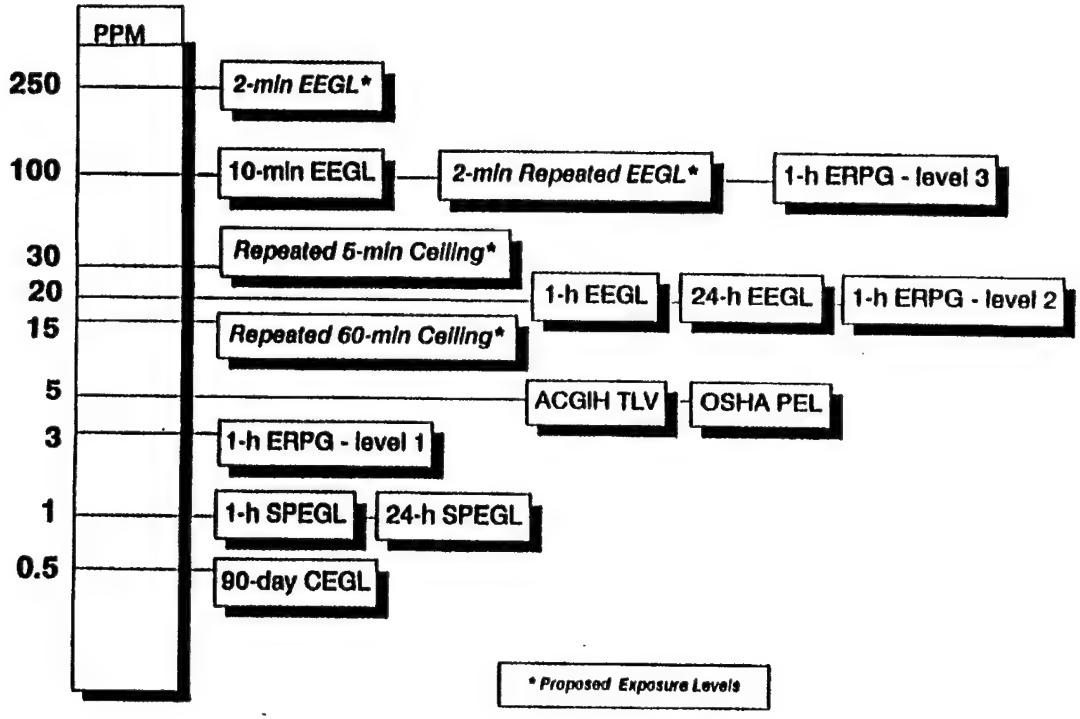

FIGURE 1 Current exposure levels for HCl.

is uncertain whether ocular irritation among personnel wearing contact lenses would be more severe at this EEGL. Therefore, although recent studies suggest contact lenses may afford some protection from irritants (Randolph and Zavon, 1987), it would seem prudent for all personnel potentially exposed at or near this level to wear protective devices such as goggles. It is noted that current U.S. Army procedures prohibit contact lens use during training and combat (U.S. Army Regulation 40-5, Paragraph 5-15 [a12]).

The EEGL of 250 ppm for HCl assumes that the 2-min exposure would be a rare event. If 2-min exposures are repeated, the level must be reduced. Based on data from exposures in baboons, repeated 2-min exposures at 100 ppm, not to exceed six times daily for 14 days, although irritating, appear unlikely to produce permanent injury or reduce efficiency in performance of tasks.

SUBCOMMITTEE'S COMMENTS ON U.S. ARMY'S RECOMMENDED CEILING LEVELS FOR HCl EXPOSURE

The U.S. Army recommendations for military health exposure limits (5 and 60 min) for HCl are based on a report by Cohen and Strange (1982), which contains an analysis of the literature available at the time. The report acknowledges the lack of quantitative human data and focuses on rodent studies, with considerations such as RD_{50} values in mice playing a prominent role in establishing recommendations for intermittent human exposures.

As discussed in this report, data from studies in baboons that have become available since the evaluation by Cohen and Strange (1982) suggest that high levels of HCl for short periods are well tolerated with respect to effects on pulmonary function. The use of the baboon data is desirable given their similarity to humans in respiratory response. Thus, intermittent human exposure to levels near 15-30 ppm would not be likely to cause pulmonary injury. However, because most animal studies have used acute exposures to high concentrations of HCl, confidence is reduced when using these data to derive values for repeated exposures. Therefore, eye and upper respiratory tract irritation severe enough to detract from performance should be a primary consideration in assessing short-term repeated exposures. In that regard, the Army's recommendations appear to be reasonable.

The subcommittee's comments on the Army's recommended 5-min ceiling of 30 ppm, not to exceed six times daily for 14 days, are as follows:

Based on recent data on baboon exposures, pulmonary effects from HCl would not be expected at exposures of up to 500 ppm for 15 min. However, repeated exposure to such levels would be expected to produce significant eye and upper respiratory tract irritation that might interfere with performance of tasks. Respiratory tract injury should not be a primary concern at lower exposure levels. Personnel would be expected to perform adequately for short periods, such as 5 min several times per day, at concentrations of HCl up to 30 ppm. The upper limit of tolerance for irritation based on qualitative human experience might be as high as 50-100 ppm for 1 hr, but data are inadequate to support exposure levels of this magnitude. Although baboons appeared able to function adequately at even higher concentrations, it is uncertain whether significant irritation would have occurred with repeated exposures. Therefore, the subcommittee concurs with the 5-min ceiling of 30 ppm.

The subcommittee's comments on the Army's recommended 60-min ceiling of 15 ppm, not to exceed six times daily for 14 days, are as follows:

This exposure scenario would have a duration similar to an 8-hr workplace exposure. The ACGIH's TLV for HCl is 5 ppm as a ceiling level. Prolonged exposure at 15 ppm, although not at a concentration expected to produce permanent injuries to eyes or respiratory tract, would be a concern if sensory irritation ultimately reduced efficiency or prevented adequate performance of tasks. Nevertheless, based on qualitative human experience, the subcommittee concurs with the 60-min ceiling of 15 ppm.

The subcommittee agrees with the U.S. Army's recommendation that additional research on the health effects of HCl exposure would be necessary to more precisely define acceptable exposure conditions for field personnel. Ideally, this research would focus on the respiratory effects of short-term, intermittent exposures to HCl, with serious consideration given to selection of test species. In addition, the subcommittee agrees that toxicological studies should be designed after adequate information on field-exposure assessment and hazard characterization is available. The subcommittee also recommends that human-effects data be collected through clinical assessments of personnel exposed to HCl.

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